Blastovin® Teva
Solution for Injection

93.131.036-C

SUMMARY OF PRODUCT CHARACTERISTICS

Blastovin® Teva
Solution for Injection
For I.V. Injection

1. NAME OF THE MEDICINAL PRODUCT
Blastovin® Teva

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial of 10 ml contains 10 mg of vinblastine sulfate.
1 ml of solution for injection contains 1 mg vinblastine sulfate.
Excipient with known effect:
Sodium chloride.
A 10 ml vial contains 35 mg sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.
Blastovin Teva is a clear solution.
Osmolarity 286 mOsm/L; pH 3.5-5.5.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Vinblastine has proved effective in the treatment of the following neoplasms, either alone or in conjunction with other oncolytic drugs:
Frequently Responsive Malignancies:
- Generalized Hodgkin's disease (Stages III and IV, Ann Arbor modification of Rye staging system).
- Non-Hodgkin's lymphoma:
  - Reticulum-cell sarcoma.
  - Lymphosarcoma.
- Mycosis fungoides.
- Neuroblastoma.
- Histiocytosis X.

Less Frequently Responsive Malignancies:
- Choriocarcinoma resistant to other chemotherapeutic agents.
- Embryonal carcinoma of the testis.
- Carcinoma of the breast, unresponsive to appropriate endocrine surgery and hormonal therapy.

4.2 Posology and method of administration
This preparation is for intravenous use only. It should be administered only by individuals experienced in vinblastine administration.

FATAL IF GIVEN BY OTHER ROUTES. FOR INTRAVENOUS USE ONLY.

In case of mistaken administration by intrathecal route, see section 4.4.

For instructions on the use/handling of the product see section 6.6.

Before each administration a monitoring of neutrophil count is necessary.

Posology

Starting dose

Adults: It is sensible to start the therapy with a single dose of 0.1 mg/kg (or 3.7 mg/m²) I.V. once per week, followed by a leukocyte count to be performed in order to establish the sensitivity of the patient to the product.

Children: It is sensible to start the therapy with a single dose of 2.5 mg/m² I.V., followed by a leukocyte count in order to establish the sensitivity of the patient to the product.

Maintenance dose

The leukopenia as a reaction to vinblastine is variable. Therefore, it is recommended not to give the product more often than once per seven days. The daily use of low doses of vinblastine is not recommended, even if the total weekly dose would be the same as the recommended dose, since frequency and severity of toxicities may be increased. The starting dose can be increased weekly by 0.05 mg/kg (or 1.8 mg/m²) for adults and 1.25 mg/m² for children. Usual dose is 5.5-7.5 mg/m², with an average dose of 0.15 to 0.2 mg/kg or 4 to 6 mg/m² in adults. Do not further increase the dose after reaching this maximum dose, which reduces the number of leukocytes to approximately 3,000/mm³. In some patients 0.1 mg/kg (or 3.7 mg/m²) can already result in leukopenia; others require more than 0.3 mg/kg (or 11.1 mg/m²) and very rarely 0.5 mg/kg (18.5 mg/m²). However, for most patients the weekly dose will be between 0.15 and 0.2 mg/kg. When the dose of vinblastine that will cause the above-mentioned leukopenia has been established, a quantity equal to the previous dose in the schedule should be administered as a maintenance dose with weekly intervals. Thus, the patient receives the maximum dose that does not cause leukopenia. The maximum dose is 0.5 mg/kg (or 18.5 mg/m²) for adults. The usual dose for children is 7.5 mg/m²; 12.5 mg/m² has been given as a single agent.

A next dose of vinblastine may only be administered when the number of leukocytes has increased to at least 4,000/mm³, also if the dose interval of seven days has passed already. In some cases the oncolytic activity can already be noticed before the leukopenic effect. If this is the case, then there will be no need to increase the next dose. The maintenance therapy with an indeterminate duration should consist of the maximum dose that can be administered on an outpatient basis once every seven to fourteen days without reducing the leukocyte count to a dangerous level.

Dose with liver function disorders

If the liver function is abnormal on the first day of treatment, then the dose of vinblastine is 100% with a bilirubin concentrate of <25 µmol/l (or <1.5 mg/dL), 50% if this is 25-50 µmol/l (or 1.5-3.0 mg/dL). Vinblastine should not be administered when bilirubin is >50 µmol/l (or >3 mg/dL).

Dose with renal function disorders

Because the metabolism and excretion are primarily hepatic, a dose adjustment does not have to be recommended for patients with a reduced renal function.

Combination therapy

In the combination schedules the doses and frequencies can differ from the above-mentioned weekly standard doses. For the correct dosing in the combination schedules is referred to the actual medical literature.

Method of Administration

Vinblastine should only be administered intravenously and should not be administered intramuscularly, subcutaneously or intrathecally.

Intrathecal administration results in fatal neurotoxicity and is therefore contraindicated.

The needed dose of injection of vinblastine can be injected either in the tube of a running intravenous infusion or directly into the vein. The last mentioned method of administration is especially suitable for the ambulant treatment of the patient. The injection can be completed in about 1 minute, provided that the needle is well placed in the vein and that no vinblastine is injected outside the veins, which can cause cellulitis or phlebitis. In order to prevent vinblastine from extravascularization it is recommended to first flush the needle and syringe with venous blood before withdrawing the needle. If extravascularization occurs the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Vinblastine should not be diluted in large quantities of solution (e.g., 100 to 250 ml) and should not be administered as a slow infusion (30 to 60 minutes or more), because this can increase the risk of irritation. In connection with the increased risk of thrombosis, it is not recommended to administer vinblastine in an extremity in which the circulation has been obstructed or shows the inclination to obstruct due to compression or invasion of the tumour, phlebitis or varices.

If reconstituted vinblastine sulfate is supplied in a different container from the original Blastovin Teva glass vial, for instance in a syringe, then it is required to supply it in an outer container with the inscription: "solely for intravenous administration".

4.3 Contraindications
- Hypersensitivity to the active substance or to one of the other vinca-alkaloids or to any of the excipients listed in section 6.1.
- Leukopenia, not related to the tumour.
- Severe uncontrolled infection. Such infections must first be controlled with antiseptics or antibiotics before administering vinblastine sulfate.
- Intrathecal administration of Blastovin Teva.
- Lactation (see section 4.6).

4.4 Special warnings and special precautions for use
The medicinal product should only be used under strict supervision of a physician specialised in the use of oncolytics, preferably in hospitals experienced with such therapies.

Syringes containing this product should be labelled with the following text: **"FATAL IF GIVEN BY OTHER ROUTES. FOR INTRAVENOUS USE ONLY."**

Injection syringes containing this product which are not for immediate use, must be packaged in an overwrap with the text: **"DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FATAL IF GIVEN BY OTHER ROUTES. FOR INTRAVENOUS USE ONLY."**

Vinblastine sulfate may only be administered intravenously. Intrathecal administration leads to fatal neurotoxicity.

If leukopenia occurs with less than 2,000 leukocytes/mm³ after the administration of a dose of vinblastine sulfate, the patient must be carefully monitored for infections until the leukocytes have increased to normal levels. Following therapy with vinblastine, the nadir in the granulocyte count may be expected to occur five to ten days after the last day of treatment. Recovery of the granulocyte count is fairly rapid thereafter and is usually complete within another seven to fourteen days. Patients with ulcerations of the skin, cachectic or geriatric patients are more vulnerable to the effects of leukopenia induced by vinblastine. Therefore the use of vinblastine in these patients is strongly advised against. In patients with bone marrow infiltration with tumour cells, a more severe bone marrow suppression can occur after the administration of vinblastine.

Although the thrombocyte count is not usually significantly lowered by therapy with vinblastine, patients whose bone marrow has been recently impaired by prior therapy with radiation or with other oncolytic drugs may develop thrombocytopenia (less than 150,000 thrombocytes/mm³). When other chemotherapy or radiation has not been employed previously, a thrombocyte reduction below the level of 150,000/mm³ is rarely encountered, even when vinblastine may be causing significant granulocytopenia. Rapid recovery from thrombocytopenia within a few days is the rule.

The effect of vinblastine upon the red blood cell count and haemoglobin is usually insignificant when other treatments do not complicate the picture.

Stomatitis and neurological toxicity, although not common or permanent, can be disabling.

The long-term daily use of low doses of vinblastine is not recommended, even if the total weekly dose would be the same as the recommended dose. It is very important to accurately follow the prescribed dosing schedule. If quantities equal to several times the prescribed weekly dose divided over seven days are administered for a long period of time, convulsions, as well as severe and permanent damage to the central nervous system and even death occur.

Contraceptive measures should be taken by both women and men during and for 6 months after discontinuation of the treatment (see section 4.6).

There is no currently available evidence to indicate that vinblastine itself has been carcinogenic in humans, although some patients have developed leukaemia following radiation therapy and the administration of vinblastine in combination with alkylating agents. Although up to now there is no single known indication of mutagenic potency of vinblastine sulfate, caution is needed with the use of vinblastine sulfate as with all cytostatic drugs.

Cases of acute dyspnoea and severe bronchial spasms have occurred after the administration of vinca-alkaloids. These reactions occur more often when vinblastine is combined with mitomycin. An aggressive treatment may be necessary, particularly with a history of pulmonary dysfunction. These reactions can occur a few minutes to several hours after the injection of vinblastine and can occur up to 2 weeks after the administration of mitomycin. After treatment with bronchodilators, corticosteroids and oxygen most patients recover completely. However, a number of patients developed a progressive dyspnoea, which made chronic use of corticosteroids necessary. Vinblastine may not be administered again (see also section 4.5).

Caution is needed with liver insufficiency, because it is likely that delayed excretion will occur and the dose will have to be adjusted (see section 4.2).

Caution is needed in patients with ischemic heart disease.

This product is generally not recommended in combination with live attenuated vaccines, phenytoin and itraconazole (see section 4.5).

Careful monitoring of the peripheral nervous system is recommended in order to allow dose adjustments.

Elevation of the serum uric acid levels can occur during the remission-induction with lymphoma; therefore the serum uric acid levels should be monitored or suitable measures should be taken.

During treatment with vinblastine, intensive sun exposure is to be avoided.

Care should be taken to avoid contact of vinblastine with the eyes.

Orthostatic hypotension may be aggravated in elderly patients.

When suspecting inadequate secretion of ADH, serum levels of electrolytes and fluid balance should be monitored.

Constipation may occur as an undesirable effect of vinblastine sulfate; this constipation responds well to such usual measures as enemas and laxatives. Constipation may take the form of upper colon impaction and the rectum may be found to be empty on physical examination. An abdominal x-ray is useful in demonstrating this condition. A routine prophylactic regimen against constipation is recommended for patients receiving high doses of vinblastine.

Precautions to be taken with administration and reconstitution

With spillage during dissolving and/or administering the risk of skin damage and damage to the cornea exists. In such cases immediate flushing with ample amounts of water is needed. During the preparation and administration, appropriate precautions should be taken for dealing with cytostatics, such as the use of protective gloves, a facial mask and safety goggles.

Extravasation must be avoided. In case of diffusion into the surrounding tissue during the intravenous administration this can cause considerable tissue irritation. Discontinue the injection immediately and inject the possible remainder of the dose in another vein.

Local injection of hyaluronidase and the application of moderate heat to the site where extravasation took place have been applied to disperse the product and to limit the inconvenience and the possibility of cellulitis and phlebitis as much as possible.

Intrathecal administration of vinblastine sulfate results in fatal neurotoxicity.

If vinblastine sulfate is **accidentally** administered intrathecally, this treatment is recommended. In one case the progressive paralysis in an adult, who received the related vinca-alkaloid vincristine sulfate intrathecally, could be stemmed with the following treatment. The treatment must be started immediately:

1. Through a lumbar tap, spinal fluid was removed, as much as possible from a standpoint of safety.
2. The subarachnoidal space was flushed with Ringer's lactate solution by continuous infusion through a catheter in a cerebral lateral ventricle at a rate of 150 ml per hour. The fluid was removed through lumbar access.
3. As soon as this became available, 25 ml of recently frozen plasma was diluted in 1 litre of Ringer's lactate solution and the dilution was infused through the cerebral ventricular catheter at a rate of 75 ml per hour. The liquid was removed again through the lumbar access. The infusion rate was adjusted in such a way that a protein level of 150 mg/ml was maintained in the spinal fluid. The treatment starting from step 3 was now repeated with again one litre diluted recently frozen plasma.
4. 10 g of glutamic acid was administered intravenously in 24 hours, followed by 500 mg orally 3 times per day for 1 month or until the neurological dysfunction stabilised. The role of glutamic acid in this treatment is not clear. Glutamic acid is possibly not essential.
5. Folinic acid was administered intravenously as a 100 mg bolus and then infused at a rate of 25 mg/h for 24 hours, then bolus doses of 25 mg every 6 hours for 1 week.

Pyridoxine was given at a rate of 50 mg every 8 hours by intravenous infusion over 30 minutes. Their roles in the reduction of neurotoxicity are unclear.

Blastovin Teva contains sodium

This medicinal product contains 35 mg sodium per vial, equivalent to 1.75% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interactions with other medicinal products and other forms of interaction
Due to the increase of thrombotic risk in case of tumoral diseases, the use of anticoagulative treatment is frequent. The high intra-individual variability of the coagulability during diseases and the possible interaction between oral anticoagulants and anticancer chemotherapy require, if it is decided to treat the patient with oral anticoagulants, an increase in the frequency of INR (International Normalised Ratio) monitoring.

The combination of vinblastine with other myelotoxic or neurotoxic agents or with radiation to larger areas increases the risk of toxicity. When chemotherapy is being given in conjunction with radiation therapy at an angle which includes the liver, the use of vinblastine should be delayed until radiation therapy has been completed.

Vinblastine sulfate must be administered with caution in patients who concomitantly take medicinal products of which it is known that they inhibit the medicinal product metabolism via iso-enzymes of the hepatic cytochrome CYP3A, or in patients with liver function disorders. The concomitant administration of vinblastine sulfate and an inhibitor of this metabolic route can cause a faster occurrence and/or increased severity of side effects.

The concomitant oral or intravenous use of digitoxin and combinations of chemotherapeutic drugs including vinblastine sulfate can lead to reduced blood levels of digitoxin, thereby lowering the efficacy of digitoxin.

The concomitant oral or intravenous use of phenytoin and combinations of chemotherapeutic drugs including vinblastine sulfate can lead to reduced blood levels of phenytoin and to a greater frequency of attacks. The dose adjustment of phenytoin should occur on the basis of the blood level. The contribution of vinblastine sulfate to this interaction is not clear. The interaction is possibly the result of a reduced absorption of phenytoin and an increase in the metabolism and elimination rate.

With the combination vinblastine and mitomycin a severe, sometimes irreversible pulmonary toxicity has been described, particularly in already injured tissue (see section 4.4). Vinblastine used as part of a combination regimen with mitomycin may result in acute respiratory distress and pulmonary infiltration. Cases of respiratory distress with interstitial pulmonary infiltrates have been reported in patients given a regimen comprised of vinblastine sulfate, mitomycin, and progesterone (MVP).

Co-administration of cisplatin has been reported to cause higher plasma concentrations of vinblastine sulfate.

There have been reports of Raynaud's phenomenon and gangrene following concomitant administration of vinblastine and bleomycin, and other vascular adverse reactions (such as myocardial infarction and cerebrovascular accident) following concomitant treatment with vinblastine, bleomycin and cisplatin.

The neurotoxicity of cisplatin or interferon and the cardiotoxicity of interferon can be potentiated by vinblastine.

Pharmacodynamic as well as pharmacokinetic interactions of vinblastine with *other cytostatics and immunosuppressive drugs* may occur, causing a reinforcement of therapeutic and toxic effects.

Interaction with radiation is also possible during and after radiation therapy.

Erythromycin may increase the toxicity of vinblastine.

Concomitant use of vinblastine and itraconazole can increase the risk of neurotoxicity or paralytic ileus.

Serum levels of anticonvulsants may be reduced by cytotoxic medications, including vinblastine.

Vinblastine may promote the cellular uptake of *methotrexate*. Interactions between vinblastine, *alkylating agents* and methotrexate during the cell cycle may result in an increase of total cytotoxic effect.

Patients receiving immunosuppressive chemotherapy should not be vaccinated with a live vaccine due to the risk of systemic, possible fatal diseases. This risk is increased in patients who are already immunosuppressed by their underlying disease. Use an inactivated vaccine when available.

4.6 Fertility, pregnancy and lactation
Pregnancy

There is insufficient data about the use of vinblastine during human pregnancy. The pharmacological action indicates potential harmful effects during pregnancy. Preclinical studies have shown genotoxicity, teratogenicity and

other reproductive toxicity (see section 5.3). Vinblastine should not be used during pregnancy unless clearly necessary.
If treatment with vinblastine is absolutely necessary during pregnancy or if pregnancy occurs during treatment, the patient should be informed about the risks for the unborn child and be monitored carefully. The possibility of genetic counselling should be considered.

Breastfeeding
It is not known if vinblastine is excreted in breast milk. Vinblastine is contraindicated during breastfeeding. Breastfeeding should be discontinued during the treatment with vinblastine.

Contraception
Men and women of childbearing age should take effective contraceptive measures during and for at least 3 months but preferably 6 months after treatment with vinblastine.

Fertility
Vinblastine can affect fertility in both men and women. As for many medicinal products, information is missing with respect to the effects of vinblastine on the spermatogenesis. Aspermia has been described in humans. Animal studies indicate an interruption of the cell division in the metaphase and degenerative changes in the germ cells (see section 5.3). Reversible and irreversible infertility in both men and women is possible after treatment with vinblastine. Amenorrhoea has occurred in some patients treated with vinblastine in combination with other drugs. Recovery of menses was frequent. Men should seek advice on conservation of sperm prior to treatment with vinblastine.

4.7 Effects on ability to drive and use machines
There are no known data about the effect of this product on the ability to drive. Considering the side effects, the possibility that this product does influence the ability to drive should be taken into account.

4.8 Undesirable effects
In general, the frequency of the adverse reactions with the use of vinblastine sulfate appears to be connected to the used dose. Most adverse reactions generally do not last longer than 24 hours.
The adverse reactions below are classified according to the following frequencies:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders
Very common
Leukopenia is the most frequent side effect and is normally the dose-limiting factor.
Common
Anaemia, thrombocytopenia and myelosuppression.
Not known
Haemolytic anaemia.

Endocrine disorders
Rare
SIADH (syndrome of inappropriate ADH secretion) has been reported with both the recommended and the higher doses (see also section 4.9).

Psychiatric disorders
Uncommon
Depression.
Not known
Psychosis.

Nervous system disorders
Common
Paraesthesia, loss of deep tendon reflexes.
Rare
Numb feeling, peripheral neuritis, headache, convulsions, dizziness. Cases of cerebrovascular accident (CVA) have been reported in patients who received the combination chemotherapy of bleomycin and cisplatin and vinblastine.
Not known
Neurogenic pain (i.e., in face and jaw), peripheral neuropathy, vocal cord paralysis.

Eye disorders
Not known
Severe epithelial erosions with blepharospasmus, swelling of the eyelid and pre-auricular lymph nodes after contact with the cornea.

Vestibular disorders
Rare
Ototoxicity, vestibular and auditory damage to the eighth cranial nerve. Manifestations include partial or total deafness, which may be temporary or permanent, and difficulties with balance, including dizziness, nystagmus and vertigo.
Not known
Tinnitus.

Cardiac disorders
Rare
Sinus tachycardia, angina pectoris, AV blockade, arrhythmia.
Not known
Cases of a myocardial infarction have been reported in patients who received the combination chemotherapy of bleomycin and cisplatin and vinblastine.

Vascular disorders
Not known
Incidental hypertension and severe hypotension have been observed. Cases of Raynaud's phenomenon have been reported in patients who received combination chemotherapy with bleomycin and cisplatin and vinblastine for the treatment of testicular tumours.
Orthostatic hypotension.

Respiratory system, thoracic and mediastinal disorders
Uncommon
Pharyngitis.
After the use of vinca-alkaloids, acute shortness of breath (bronchospasms) has been reported. In patients who concomitantly or previously were treated with mitomycin, dyspnoea, rhonchi, infiltrative abnormalities and a lung function disorder can occur a few minutes to several hours after the administration of vinblastine and can occur up to 2 weeks after the administration of mitomycin, based on the pulmonary toxicity of this combination. Both products must then be discontinued immediately (see sections 4.4 and 4.5).

Gastro-intestinal disorders
Very common
Nausea, vomiting.
Common
Constipation (see section 4.4), ileus, bleeding from an old peptic ulcer, haemorrhagic enterocolitis, rectal blood loss, anorexia and diarrhoea.
Not known
Stomatitis, gastric pain, abdominal pain, tender parotid glands.

Hepatobiliary disorders
Not known
Liver fibrosis.

Skin and subcutaneous tissue disorders
Very common
Hair loss; this is usually not complete and in a number of cases the hair growth starts again during the maintenance therapy.
Blister formation in the mouth and on the skin has been reported.
Not known
Dermatitis, phototoxicity.

Musculoskeletal, connective tissue and bone disorders
Not known
Muscular atrophy.

Renal and urinary disorders
Not known
Urinary retention, thrombotic microangiopathy with renal insufficiency.

Reproductive system and breast disorders
Not known
Fertility decreased, aspermia.

General disorders and administration site conditions
Uncommon
Pain at the site of the tumour, malaise.
Not known
Weakness, fever, extravasation in the subcutaneous tissue during the intravenous injection of the vinblastine solution can lead to cellulitis, necrosis and thrombophlebitis, pain at the injection site especially after injection in small vessels.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il.

4.9 Overdose
Symptoms
Overdosing with vinblastine sulfate results in an aggravation of undesirable effects (see section 4.8). Bone marrow suppression in leukopenia may be more pronounced. In addition, neurotoxicity (paraesthesia, peripheral neuropathy) similar to that seen with vincristine sulfate may be observed.

Treatment
There is no antidote for vinblastine. Treatment is symptomatic and supportive.
Discontinuation of vinblastine administration is advised. If necessary, general supportive measures should be taken and a blood transfusion should be given. In case of an overdose the following treatment is recommended:
1. Prevention of the effects of the "inappropriate ADH syndrome" by fluid limitation and the administration of a diuretic acting on the loop of Henle and distal tubule function.
2. Administration of an anti-convulsive drug.
3. Liquid food on account of possible ileus.
4. Cardiovascular monitoring.
5. Daily haematological evaluation.
6. Animal studies have indicated that folic acid may have a protective effect, for which the following schedule can be maintained:
   100 mg I.V. every 3 hours for 48 hours and every 6 hours the next 48 hours.

Haemodialysis does not appear effective in removing the medicinal product.
Based on the pharmacokinetic data it can be expected that elevated levels will remain for at least 72 hours.
If vinblastine is swallowed, activated charcoal in a water slurry may be given by mouth along with a cathartic. The use of cholestyramine in this situation has not been reported.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic category: Oncolytics, vinca-alkaloids and derivatives.
ATC-code: L01CA 01
Vinblastine belongs to the vinca-alkaloids, binds to tubulin and disrupts the microtubular function both by preventing polymerisation and by inducing depolymerisation of formed microtubules. This disturbs the normal reorganisation of the microtubule network, which is needed for interphase and mitosis. In addition to an arrest in mitosis, vinca-alkaloids also seem to be cytotoxic to non-proliferating cells in the G1- and S-phase.
Haematological effects: during treatment with vinblastine a leukopenia can be expected; the leukocyte count is an important guideline for the therapy. In general, the leukopenia will be more pronounced and will last longer as the administered dose is larger.
After the initiation of the therapy with vinblastine, the leukocyte count will be expected to be lowest 5-10 days after the last day of the medication. After this the leukocyte count recovers reasonably fast (within 7-14 days). With the lower doses for maintenance therapy leukopenia is usually not a problem. Although the number of thrombocytes usually does not drop significantly due to the treatment with vinblastine, sporadically a severe thrombocytopenia can occur, although less frequently than with other cytostatics.
In patients with bone marrow inhibition due to prior radiation therapy or treatment with another oncolytic, thrombocytopenia (fewer than 200,000 thrombocytes per mm^3) can occur. If radiation therapy or other chemotherapy has not been administered before, then the thrombocyte count will rarely drop below the level of 200,000 per mm^3, even when vinblastine causes an evident leukopenia. A rapid recovery of the thrombocytopenia within a few days is the rule. The effect of vinblastine on the erythrocyte count and the HB level is usually insignificant, provided that a different therapy does not complicate the picture.

5.2 Pharmacokinetic properties
Vinblastine has a large distribution volume; this can be 27.3 litres/kg. Studies in rats showed that the highest concentrations of radioactivity were found in the lungs, the liver, the spleen and the kidneys 2 hours after injection of labelled vinblastine. Vinblastine is to a great degree bound to serum proteins (>99%). Vinblastine is metabolised into the active deacetyl vinblastine.
Vinblastine shows a reduction of the serum concentration after a rapid intravenous injection in three phases (with large inter- and intra-individual variability):
- a very rapid steep reduction in concentration (alpha-phase, half-life 4 minutes)
- a rather brief middle period (beta-phase, half-life 1.6 hours)
- the much longer-lasting end phase (gamma-phase, half-life 25 hours with a range from 17-31 hours)

As the most important route of excretion could be via the bile, the toxicity of this medicinal product can be increased with abnormal excretion via the bile. After injection of labelled vinblastine in patients, 10% of the radioactivity was recovered in the faeces, 14% in the urine, while the remaining radioactivity could not be recovered. Systemic clearance is 0.74 l/kg/hour.
Vinblastine crosses the blood-brain barrier poorly and does not appear in the CSF in therapeutic concentrations after intravenous administration.

5.3 Preclinical safety data
Animal studies with respect to reproduction have shown harmful effects on fertility as well as embryo toxicity. Chronic toxicity studies have shown inhibition of spermatogenesis and gastro-intestinal toxicity. Various genotoxicity tests have shown that vinblastine can induce chromosomal abnormalities, micronuclei and polyploidy. Vinblastine is possibly carcinogenic. Other preclinical information does not add relevant information to that provided in the clinical sections.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium chloride
Water for injections

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except for those mentioned in section 6.6.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.
Chemical and physical in-use stability has been demonstrated for 6 hours at room temperature (15-25°C) in ambient light when diluted to a concentration of 0.5 mg/ml in NaCl 0.9% or Glucose 5%.
From a microbiological point of view the product should be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
Store in the refrigerator (2-8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container
10 ml solution in a colourless type I glass vial with a bromobutyl rubber stop with an aluminium white snap-cap.
Each carton contains a single vial.

6.6 Special precautions for disposal and other instructions
Administration
Vinblastine should be administered only by or under the direct supervision of a qualified physician who is experienced in the use of chemotherapeutic agents.

Preparation
Chemotherapeutic agents should be prepared for administration only by professionals who have been trained in the safe use of the preparation.
Reconstitution of powder and transfer to syringes should be carried out only in the designated area.
The personnel carrying out these procedures should be adequately protected through clothing, gloves and eye shield.
Pregnant staff should not handle cytotoxic agents.
Blastovin Teva can be diluted in NaCl 0.9% or Glucose 5% to a concentration of 0.5 mg/ml and be administered intravenously. The solution must be prepared immediately before use.
Blastovin Teva does not contain a preservative and is consequently only suitable as product for single use.

Contamination
In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline solution. An emollient cream may be used to treat the transient stinging of skin. Medical advice should be sought if the eyes are affected.
In the event of spillage, employees should put on gloves and mop up the spilled material with a sponge kept in the area for that purpose. Rinse the area twice with water. Put the spilled solutions and sponge into a plastic bag and seal it.
Excrements and vomit must be cleaned up with care.

Disposal
Syringes, vials, absorbent materials, solution and any other contaminated material should be placed in a thick plastic bag or other impervious container and incinerated. Any unused product, damaged vials or contaminated waste material must be placed in waste containers specifically intended for this purpose and disposed of in accordance with local requirements.

7. LICENCE HOLDER AND MANUFACTURER
Licence Holder:
Abic Marketing Ltd.,
POB 8077, Netanya.

Manufacturer:
Pharmachemie B.V. (Teva Group),
Haarlem, The Netherlands.

8. REGISTRATION NUMBER
146.63.33376

This leaflet format has been determined by the Ministry of Health and the content has been checked and approved by the Ministry of Health in March 2016 and updated according to the guidelines of the Ministry of Health in February 2020.